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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
JOHN SHIGEURA and JER-KANG CHEN

Appeal 2008-4069
Application 09/908,994
Technology Center 1600

Decided: September 24, 2008

Before DEMETRA J. MILLS, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for isolating different-sequence polynucleotides from a mixture. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

BACKGROUND

"To analyze multiple polynucleotide sequences in a sample, it is desirable to use as few reaction vessels as possible in order to use reagents efficiently and reduce liquid manipulations" (Specification 1).

> More generally, it is often desirable to simultaneously generate a plurality of polynucleotide populations in a single reaction mixture, followed by isolation of the different populations from the mixture for further analysis or manipulation. Ideally, such a method should be convenient to perform and should allow the isolation and separation of the different polynucleotide populations in analytical or preparative amounts.

(*Id.* at 2.)

The Specification discloses "methods whereby the separation and isolation of different polynucleotide populations can be achieved using a single flow path" (*id.*).

DISCUSSION

1. CLAIMS

Claims 21-38 are pending and on appeal. Claim 21 is representative and reads as follows:

Claim 21: A method for isolating one or more different-sequence polynucleotides from a mixture, the method comprising:

(a) flowing the mixture through a flow path containing a plurality of solid supports which are located in series in the flow path, such that the mixture flows serially through each of the plurality of solid supports, each support having bound thereto a sequence-specific capture agent complementary to a different-sequence polynucleotide, under conditions effective to specifically bind different-sequence polynucleotides to corresponding sequence-specific capture agents on one or more of the supports,

(b) after step (a), releasing bound polynucleotides from a selected support by altering a physical property of that support while leaving unaltered the same physical property of at least one other of the supports,

wherein the physical property is temperature, and wherein said releasing is accomplished by heating a first solid support; and

(c) eluting the released polynucleotides through the flow path such that the eluted polynucleotides can be isolated in separated form.

2. OBVIOUSNESS

Claims 21-38 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Zanzucchi,[1] Okano[2] and Brenner.[3]

The Examiner relies on Zanzucchi as disclosing "a method of isolating one or more different-sequence polynucleotides from a mixture" and "using an array of wells in serial fluid connection, through which a sample is caused to pass" (Answer 5). The Examiner further finds that Zanzucchi discloses "heating and cooling means in the well as well as the use of pumping means to move a sample from one well to another" and "conducting PCR wherein the primer is immobilized to a solid support" (*id.*).

The Examiner relies on Okano as disclosing "a polynucleotide capturing chip" in which "the combination of heating and reversal of electric field can be used to achieve elution of specifically captured sequences from specific wells/regions of the chip, while retaining the captured polynucleotide bound at other positions" (*id.* at 6). The Examiner reasons that "[w]hile Okano et al., uses a single substrate, it has been fashioned into a series of cells, and the temperature and electric field of each is under

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[1] Zanzucchi et al., US Patent No. 5,593,838, Jan. 14, 1997.
[2] Okano et al., US Patent No. 5,607,646, Mar. 14, 1997.
[3] Brenner, US Patent No. 5,962,228, Oct. 5, 1999.

control, thereby allowing for individual, serial, or simultaneous elution of released polynucleotides" (*id.*).

The Examiner relies on Brenner as disclosing that "an array can be fashioned from a plurality of microparticles that are brought into contact with a support" (*id.*).

The Examiner concludes that

> it would have been obvious to one of ordinary skill in the art …to have combined the microparticles of Brenner in the individual cells of the array of Okano et al., with the series of wells/array of Zanzucchi et al., whereby the device would be used in a polynucleotide assay whereby specific binding reactions can take place at selected supports and eluted from same, and that the mixture would flow in a serial fashion through each of the solid supports.

(*Id.* at 6-7.)

Appellants argue that the references do not teach the recited step (b) after step (a) (Appeal Br. 10). That is, claim 21 requires that "the mixture flows through all of the relevant solid supports (where each capture agent in the plurality of supports can bind to a polynucleotide that may be present in the sample) before one commences step (b)" (*id.*) and Appellants argue that "Zanzucchi teaches that each of the wells allows for a subsequent action upon a product from the previous well, suggesting that Zanzucchi's method involves the stepwise action upon a single evolving product" (*id.* at 10-11).

Appellants also argue that Zanzucchi discloses that heating the wells results in the sealing of the wells by valves, which would prevent the mixture from flowing out until the solution has cooled and the polynucleotides have re-annealed (*id.* at 14). Appellants argue that this deficiency is not remedied by Okano because "Okano does not teach the use

of specific heat (*e.g.*, at a specific location), but rather the use of general heat *(e.g.,* throughout the solution) combined with specific electrical changes" (*id.* at 15).

We agree with Appellants that the Examiner has not adequately shown that the method of claim 21 would have been obvious based on the disclosures of Zanzucchi and Okano. Zanzucchi discloses a "system for processing a plurality of tests or syntheses in parallel" (Zanzucchi, abstract). Fig. 1B of Zanzucchi is shown below:

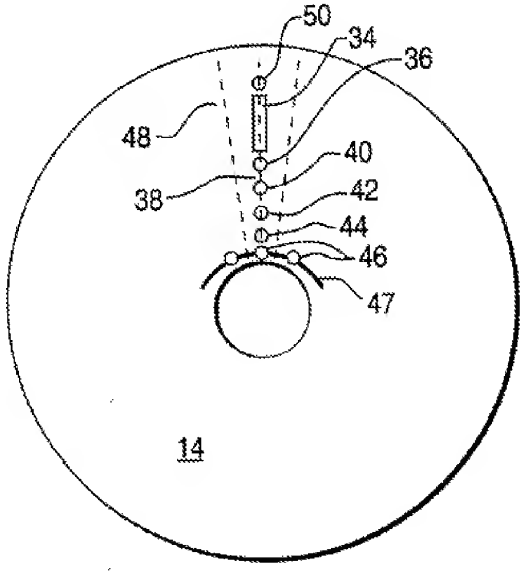

FIG. 1B

Fig. 1B is said to show "a top view of a substrate of the invention illustrating a single module formed therein" (*id.* at col. 3, ll. 15-16).

> Zanzucchi also discloses that in one exemplary embodiment,
>
> in the first well **36** the whole blood sample is transferred from the capillary loading channel **34**, filtered and lysed to separate the white and red corpuscles, and the DNA is isolated from the white blood cells. The DNA sample is then moved out of the first well **36** through a connecting channel **38** that connects all of the wells of a single module, and into a second well **40**. In

> the second well **40** the DNA is separated into single strands and amplified using the well known PCR method. The treated sample is then moved out of the second well **40** via the connecting channel **38** and into a third well **42**. In the third well **42** the DNA is assayed by known probe hybridization techniques. The DNA assay is detected and evaluated in the fourth well **44**. Thus the determination of DNA in a particular blood sample is performed in a series of four wells connected by a channel. Lastly excess reagents and the like are collected in the fifth well **46** ….

(*Id.* at col. 4, ll. 36-53.)

Okano discloses a "method for simultaneously detecting a plurality of target polynucleotides in a sample on a single reaction chip and a method for separating a plurality of target polynucleotides" (Okano, abstract). Okano discloses that the "target polynucleotides captured onto the chip via a hybridization reaction are readily eluted via heating and the like. . . . [A]n electric field can be applied sequentially to individual cells so as to elute a target polynucleotide captured onto each of the cells." (Okano, col. 3, ll. 15-20.) That is,

> [i]n a cell applied with a positive electric field, the addition of a heated eluent cannot trigger the elution . . . of the target polynucleotide because of the negative charge thereof. If the electric field applied to the cell is switched to negative, the target polynucleotide is eluted via electrostatic repulsion. The sequential switch-over of the electric field regarding all the cells one by one enables the elution and recovery individually of different target polynucleotides.

(*Id.* at col. 3, ll. 20-28.) "Thus, it is possible to recover the captured target polynucleotide if heating is effected at a predetermined temperature. As has been described above, a plurality of target polynucleotides can be recovered

without contamination, by switching the electric field applied to a cell one by one on the reaction chip." (*Id.* at col. 4, ll. 5-10).

Okano describes the process of eluting and recovering captured polynucleotides in its Example 3. In that Example, "five fragments are captured among the six Hind III fragments. While applying an electric field so as to maintain each cell as positive electrode . . . , a separation solution . . . is added from the sample addition part **93** for heating to 65° C. to 70° C. *The separation solution then covers the reaction container in its entirety*." (*Id.* at col. 9, ll. 46-53, emphasis added.)

Okano teaches that switching the electric field in the cells one by one prevents the polynucleotides from eluting until a positively charged capillary is inserted into each cell to recover the polynucleotide immobilized therein (*see id.* at col. 9, ll. 57-67).

We agree with Appellants that the Examiner has not adequately explained how the cited references would have suggested the method defined by instant claim 21. In particular, the Examiner has not explained why the references would have made it obvious to flow a mixture of polynucleotides past a series of supports before changing the temperature of at least one of the supports while leaving the temperature of others unchanged.

As discussed above, Okano changes the temperature of all of the cells in its device at the same time, and then elutes the polynucleotides individually based on electrostatic attraction and repulsion. Okano does not teach changing the temperature of cells individually.

Zanzucchi does teach changing the temperature of wells individually, but only in the context of a process involving the polymerase chain reaction (PCR), a process in which the solution does not flow past a plurality of supports, having different oligonucleotides attached, before the temperature is changed, as required by claim 21. The Examiner cites Brenner only for its disclosure of an array fashioned from microparticles (Answer 6), not for any disclosure suggesting heating individual cells or supports in an array.

Thus, none of the references relied on by the Examiner teach a process in which a mixture of polynucleotides is flowed past a series of supports and then the temperature of one or a subset of the supports – but not all of them – is changed. Nor has the Examiner adequately explained why such a process would have been obvious based on the cited references.

SUMMARY

The Examiner has not adequately shown that the cited references would have made obvious the method of claim 21 to a person of ordinary skill in the art. Claims 22-38 depend on claim 21. We therefore reverse the rejection of claims 21-38 under 35 U.S.C. § 103(a).

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

REVERSED

cdc

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